PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 101063-1 WO	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/GB2004/002723	International filing date *(day/month/year)* 24.06.2004	Priority date *(day/month/year)* 30.06.2003

International Patent Classification (IPC) or national classification and IPC
INV. A61K31/53 C07D251/48 C07D251/54 C07D251/52 C07D239/48 C07D401/12 C07D403/12 C07D401/14 C07D417/14 A61K31/505 A61K31/506 A61K31/4427 A61P25/28 C07D251/00

Applicant
ASTRAZENECA AB et al.

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 135 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in celectronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☒	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☒	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
20.04.2005	15.05.2006
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Gavriliu, D Telephone No. +49 89 2399-

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/GB2004/002723

Box No. I Basis of the report

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.

PCT/GB2004/002723

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-8(part), 10-17(part.), 19-29(part.), 31-39(part.), 41-43(part.), 44-46, 47-49(part.)

because:

☒ the said international application, or the said claims Nos. 44-46 relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the whole application or for said claims Nos. 1-8(part.), 10-17(part.), 19-29(part.), 31-39(part.), 41-43(part.), 47-49(part.)

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.

PCT/GB2004/002723

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:

   ☒ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ not paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☒ complied with

   ☐ not complied with for the following reasons:

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☒ all parts.

   ☐ the parts relating to claims Nos.

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	9, 18, 40
	No:	Claims	1-8, 10-17, 19-39, 41-49
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-49
Industrial applicability (IA)	Yes:	Claims	1-43, 47-49
	No:	Claims	

2. Citations and explanations

see separate sheet

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.

PCT/GB2004/002723

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

   and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

   see form 210

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

For reasoning with regards to unsearched subject-matter, see Form PCT/ISA/210 of the International Search Report. No International Preliminary Examination will be carried out with respect to subject-matter which is not covered by the search report (Rule 66.1(e)PCT).

Present Claims 1 and 19 relate to an extremely large number of possible compounds. In fact, the above-mentioned claims contain so many options, variables, possible permutations that a lack of clarity (and conciseness) within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT arises to such an extent as to render a meaningful search of the Claims 1 and 19 impossible. The Claims 1 and 19 can in no way be considered to be a reasonable generalisation of the actual examples since it include numerous possibilities which cannot be considered as equivalents, homologues or analogues of the examples. Consequently, the search was carried out for those parts of the application which do appear to be clear (concise and supported by the examples), namely:

- in the case of Claim 1 for the compounds for which R4 is COOCH3 , CONHCH2CH3, CONHCH2heterocycle or the compounds of formula (I) are substituted in position 2 with a 2-amino-4-methyl-pentan-1-ol. All the compounds claimed by Claim 18 have been searched.

-in case of Claim 19 for the compounds for which R4 is COOCH3 , -CONH- or CO-heterocycle for the compounds of formula (II). All the compounds claimed by Claim 40 have been searched.

Exactly the same objections arise for substantive examination. It should be noted that if the incomplete search objection were not made there would be a much greater objection to be made re lack of unity of the subject-matter claimed by the present Claim 1 as well as for the subject-matter claimed by the present Claim 19. It is pointed out that for being considered as unitary all the compounds falling under the general structure (I) claimed by the Claim 1 should share a significant element structure. This is not the case for the present application since the common element for the compounds of formula (I) is only the nitrogen atom linked on the heterocycle structure and further

substituted with a CH moiety.

Claims 44-46 relate to subject-matter considered by this Authority to be covered by the provision of Rule 67.1(iv)PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims(article 34(4)(a)(I)PCT).

Re Item IV
Lack of unity of invention

The separate inventions of the present applications are:

1. Compounds of formula (I), their pharmaceutical compositions and uses.

2. Compounds of formula (II), their pharmaceutical compositions and uses.

The present application discloses compounds of formula (I) or (II), useful for treating neurodegenerative diseases associated with beta-amyloid production. The structural element shared by the independent Claims 1 and 19 is the 6-membered heterocycle substituted in positions 2, 4 and 6. A further unifying feature is the use of the above-mentioned compounds for the preparation of medicaments useful in treating neurodegenerative diseases. However, according to Rule 13.2 PCT the special technical feature providing a link between inventions (Rule 13.1 PCT) must make contribution over the prior art. This requirement is not fulfilled in the present application because the document WO 02/100836(D9) discloses compounds inhibiting the formation of the amyloid beta-peptide, which present the same core-structure as the formulae (I) and (II) (see compounds of Claim 1 when R4 is hydrogen and the derivatives of pirinixic acid from page 46). Consequently, the document D9 destroys the novelty of both common features.

Re Item V
Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. The opinion expressed below with regard to novelty, inventive step and industrial applicability refers only to subject-matter for which an international search report has been drawn up (i.e. Claims 1-8 part., 9, 10-17 part., 18, 19-39 part., 40, 41-

49(part.)as far as specific compounds recited in Claim 18 and Claim 40).

2. Reference is made to the following documents:

D1: DATABASE CHEMABS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; PRINS, LEONARD J. ET AL: "Diastereoselective noncovalent synthesis of hydrogen-bonded double-rosette assemblies" XP002298973 retrieved from STN Database accession no. 2002:434936

D2: DATABASE CHEMABS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; PRINS, LEONARD J. ET AL: "Complete asymmetric induction of supramolecular chirality in a hydrogen-bonded assembly" XP002298974 retrieved from STN Database accession no. 1999:255935

D3: WO 00/25780 A1 (BRISTOL-MYERS SQUIBB COMPANY, USA) 11 May 2000 (2000-05-11)

D4: EP-A1-0 834 507 (JANSSEN PHARMACEUTICA N.V., BELG.) 8 April 1998 (1998-04-08)

D5: US-A-4 281 103 (KAINMUELLER, THOMAS ET AL) 28 July 1981 (1981-07-28)

D6: WHITTEN, JEFFREY P. ET AL: "Rapid Microscale Synthesis, a New Method for Lead Optimization Using Robotics and Solution Phase Chemistry: Application to the Synthesis and Optimization of Corticotropin Releasing Factor1 Receptor Antagonists" JOURNAL OF MEDICINAL CHEMISTRY , 39(22), 4354-4357 CODEN: JMCMAR; ISSN: 0022-2623, 1996, XP002298972

D7: US-A-3 498 984 (SANTILLI ARTHUR A ET ALL) 3 March 1970 (1970-03-03)

D8: WO 01/05783 A (PAN GONGHUA ; BALDWIN JOHN J (US); DOLLE ROLAND E III (US); OHLMEYER M) 25 January 2001 (2001-01-25)

D9: WO 02/100836 A (CONNOP BRUCE P ; GRANT AMELIA (CA); ACTIVE PASS PHARMACEUTICALS IN (CA) 19 December 2002 (2002-12-19)

D10: WO 03/007963 A (NEOTHERAPEUTICS INC ; FICK DAVID B (US); FOREMAN MARK M (US); GLASKY A) 30 January 2003 (2003-01-30)

D11: WO 03/032994 A (BOEHRINGER INGELHEIM PHARMA ; DORNER-CIOSSEK CORNELIA (DE); HIMMELSBAC) 24 April 2003 (2003-04-24)

D12: WO 99/16761 A1 (MITSUBISHI CHEMICAL CORPORATION, JAPAN) 8 April 1999 (1999-04-08)

D13: DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE,

COLUMBUS, OHIO, US; GRUDZINSKI, STEFAN ET AL: "Condensation of 2,4-dichloro-6-methoxy-s-triazine (DCMT) with amines and amino acids" XP002339542 retrieved from STN Database accession no. 1978:191368

D14: WO 99/65881 A1 (NISSAN CHEMICAL INDUSTRIES, LTD., JAPAN) 23 December 1999 (1999-12-23)

D15: DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; HARRIS, ROBERT B. ET AL: "Inhibition and affinity chromatography of human serum angiotensin converting enzyme with cysteinyl-proline derivatives" XP002339543 retrieved from STN Database accession no. 1982:138706

D16: GB-A-1 405 132 (CIBA-GEIGY A.-G.) 3 September 1975 (1975-09-03)

D17: US-A-3 271 478 (D'ALELIO GAETANO F) 6 September 1966 (1966-09-06)

D18: WO 00/43369 A1 (ELAN PHARMACEUTICALS, INC., USA; AMERICAN HOME PRODUCTS CORPORATION) 27 July 2000 (2000-07-27)

D19: EP-A2-0 201 633 (ABBOTT LABORATORIES, USA) 20 November 1986 (1986-11-20)

D20: JP 55 112269 A2 (MITSUBISHI CHEMICAL INDUSTRIES CO., LTD., JAPAN) 29 August 1980 (1980-08-29)

D21: US-A-4 140 496 (OI, NAOBUMI ET AL) 20 February 1979 (1979-02-20)

D22: GB 929 426 A (IMPERIAL CHEMICAL INDUSTRIES LIMITED) 26 June 1963 (1963-06-26)

D23: DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; BRUCKNER, H. ET AL: "Design of chiral monochloro-s-triazine reagents for the liquid chromatographic separation of amino acid enantiomers" XP002339544 retrieved from STN Database accession no. 2003:428127

D24: DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; WENSCHUH, H. ET AL: "Spatially addressed SPOT-synthesis on novel polymeric membranes" XP002339545 retrieved from STN Database accession no. 2002:46906

D25: DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; SCHARN, DIRK ET AL: "Efficient parallel synthesis of 1,3,5-triazines on continuous surfaces" XP002339546 retrieved from STN Database accession no. 2002:46839

D26: DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; SCHARN, DIRK ET AL: "Spatially Addressed Synthesis of Amino- and Amino-Oxy-Substituted 1,3,5-Triazine Arrays on Polymeric Membranes" XP002339547 retrieved from STN Database accession no. 2000:355907

D27: DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; BRUECKNER, HANS ET AL: "Use of chiral monohalo-s-triazines as novel derivatizing reagents for DL-amino acids" XP002339548 retrieved from STN Database accession no. 1995:66811

D28: DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; PARASHARYA, P. M. ET AL: "Triazines: 2-(2'-anilino-1',3',4'-thiadiazol-5'-ylthi o)-4,6-di(N-arylcarbamoylmethylamino)-s-triazines" XP002339549 retrieved from STN Database accession no. 1995:64076

D29: DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; BRUECKNER, HANS ET AL:"Use of chiral monohalo-s-triazine reagents for the liquid chromatographic resolution of DL-amino acids" XP002339550 retrieved from STN Database accession no. 1993:160226

D30: DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; BRUECKNER, HANS ET AL: " Chiral mono-chloro-s-triazines as derivatizing reagents for resolving DL-amino acids by HPLC" XP 002339551 retrieved from STN Database accession no. 1992:644768

D31: WO 03/045923 A1 (SANKYO COMPANY, LIMITED) 05. June 2003 (2003-06-05)

3. Novelty (Article 33(1) and (3) PCT)

The present application describes compounds of formula (I), useful to treat neurodegenerative diseases.

The present compounds are novel over the compounds disclosed by D9 on the account of NCHR3R4 substituent, over the compounds disclosed by D10 on the account of R7-W substituent and over the compounds of D11 on the account of the 2,4 and 6 position of substitutions on the 6-membered heterocycle.

Consequently, the above-mentioned documents are disregarded for the assessments of novelty of the present application.

The triazines with rn: 225788-02-3P, 225788-01-2P disclosed by D1 and with rn 225788-02-3, disclosed by D2 are novelty destroying compounds for the present general structure(I). Examples 104-105 107-108, 111, 115-117, 119, 123, 125, 127-129, 132-134,136,137,142,143,144,146-150, 154-156, 164, 165, 177, 182, 183, 190-195, 197, 212, disclosed by D3 represent novelty destroying embodiments for the general structure claimed by the present Claim 1. Examples 18, 19, 23-25, 27, 29,30,31, 35, 63 and 65 disclosed by D4 represent specific embodiments of the general structure (I) claimed by the present application. Example 7 disclosed by D5, compounds 5u and compounds e, j, o and t from fig. 1 of D6 are novelty destroying compounds for the present general structure (I). Examples 9, 15, 16, 19, 22, 24, 27-29 disclosed by D7 are also novelty destroying compounds for the subject-matter claimed by the present Claim 1. Moreover, the structure claimed by the Claim 1 of D7 present an overlapping range with the Markush structure Claimed by the present claim 1, when the present W is Sand R4 is an optionally substituted C1-6 alkyl. The general structure disclosed by Claim 1 of D8 presents, when A1 is R4R5N-C(O) and R4 is C1-C4 alkyl substituted with a heteroaryl, an overlapping range with the present general structure (I).

D12-D30 discloses compounds which are novelty destroying for the subject-matter claimed by the Claims 19-39 (compounds of formula (II)(see search report) (invention 2).

Since D1-D8 disclose novelty-destroying compounds and overlapping ranges with the Markush structure (I) claimed by the present application (invention 1) and D12-D30 discloses novelty-destroying compounds for the general structure (II) claimed by Claim 19 (invention 2), the novelty of the subject-matter of the present Claim 1 Claim 19 cannot be acknowledged. However, the compounds claimed by the Claim 18 and Claim 40 seem to be novel over the cited prior art documents.

4. **Inventive step** (Article 33(1) and (3) PCT):

Since, the documents D1-D8 disclose compounds and general formulae which are either novelty destroying embodiments or present overlapping regions comprising

novelty destroying embodiments for the subject-matter of the Claims 1 and D12-D30 disclose compounds which are novelty-destroying embodiments for the general structures claimed by Claims 19-39, an inventive step can be discussed only for the novel compounds of the present application (e.g. for subject-matter of Claims 18 and Claim 40).

The application is concerned with 6-membered heterocycle derivatives, which inhibit the production of beta amyloid protein.

D11, which is regarded as being the closest prior art, discloses tri-substituted pyrimidines useful to treat the same diseases as in the present case (see Claims 1, 11 of D11 and pages 34-37). The compounds disclosed by D11 (e.g. the embodiments 2, 7, 10 and 11 disclosed in page 22-lines 23, 28, 31, page 23-line 1) differ from the compounds claimed by the present Claims 1 and 19 only through the position of substitution on the pyrimidine ring 2, 4 and 5 instead of 2, 4 and 6 as for the present case.

The technical problem underlying the present case, can however not to be seen in providing further 6-membered heterocycle derivatives useful to treat neurodegenerative diseases for the following reasons:

D9 and D10 and D31 discloses also pyrimidine derivatives useful to inhibit the beta amyloid production (see Claims 1 and 40 of D9 and Claim 1 and page 20-line 31-page 21-line 7 of D10 and the abstract and the compounds with rn:186627-39-6, 609789-03-9, 609789-11-9, 609789-15-3, 50892-23-4, 50892-24-5D and 54061-62-0P of D11). The compounds disclosed by D9-D11 are pyrimidine substituted in the same positions (2,4,6) as in the present case (see e.g. the Markush structure from page 8 -lines 1-3 of D9 and compounds 1, 4, 7 and 10 from page 17 of D10)

Since, the present compounds are only substituted in position 6 instead of 5 compared with the compounds disclosed by D11, and the compounds disclosed by D9-D10 are pyrimidines substituted in position 2, 4 and 6, the skilled person would have expected that the same qualitative effect would be maintained in such similar compounds.

The problem underlying the present application should thus be seen in providing

of novel pyridines, pyrimidines or triazines with unexpected or surprising effects compared to those of the closest prior art.

An inventive step cannot either for compounds of formula (I)(invention 1) or for compounds of formula (II) (invention 2) be recognized as it is not yet shown by appropriate information, e.g. in form of experimental data, that substantially all the claimed compounds have un unexpected property or significantly improved activity over the structurally closest prior art compounds, which is attributable to the distinguishing feature of the invention.

5. **Industrial applicability** (Article 33(4)PCT).

For the assessment of the present Claims 44-46 on the question whether they are industrial applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may also allow, however, claims to a known compound for the manufacture of a medicament for a new medical treatment.

Re Item VI

Certain documents cited

Certain published documents

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*
WO03/066099	14.08.2003	03.02.2003	05.02.2002